

A FOCUS MEETING REPORT FROM:

2nd Expert Workshop on Parathyroid Disorders

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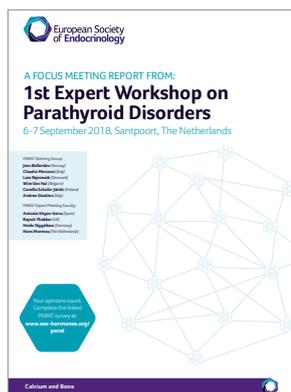


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Resources



This report provides readers with:

- Consensus Statement Abstract of 1st Expert Workshop, 2018
- Summaries of each faculty presentation
- Key learning points emerging from our topical discussions
- Key recommendations or practical solutions required

For those seeking a deeper understanding of parathyroid disorders, or for teaching and training purposes, a set of further digital materials is available at www.ese-hormones.org/parat, including:

- 2019 2nd Expert Workshop report with live references to PubMed
- Presentation summary transcripts
- Faculty slide sets (where permitted)
- 2018 1st Expert Workshop report

When referring to any materials obtained from the PARAT webpages, please cite:

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Welcome

What is PARAT?

PARAT is an ESE Calcium and Bone Focus Area programme, that is identifying the challenges and unmet research and clinical needs of parathyroid disorders.

It is led by a Steering Group and invited Faculty and participants, who together are proposing new actions and solutions to alleviate these disorders, through:

- **Expert workshops**
- **Community events**
- **Digital communications**
- **Educational reports**
- **Official publications**
- **Defining research gaps**

For more resources and to get involved, visit

www.ese-hormones.org/parat

On behalf of the European Society of Endocrinology and my fellow Steering Group colleagues, we are delighted to publish this summary report of the 2nd Expert Workshop on Parathyroid Disorders, held earlier this year.

Building on the outcomes of the first Expert Workshop held in September 2018, the forum welcomed back twenty 2018 participants, who were joined by a further forty invited expert endocrinologists, surgeons and pathologists, from 23 countries. Through expert presentations and group synthesis sessions, delegates shared their opinions, research ideas and management experiences, to identify how to overcome the unmet needs of parathyroid patient care.

After 24 hours of intense discussions, we collated the group's list of recommendations, approaches or practical solutions that PARAT stakeholders and others could consider next. Our combined suggestions of how to improve management practices and education of hypoparathyroidism, hyperparathyroidism and other parathyroid disorders are presented on pages 22-26 of this report.

Whether an endocrinologist, endocrine surgeon, pathologist, trainee or other health care professional, we look forward to working with you all to continue our quest to improve the future care of parathyroid disorder patients through the PARAT programme.

I would like to thank all Steering Group colleagues, faculty, speakers and participants for achieving another high quality, thought provoking event and for their continuing work as PARAT expert ambassadors to action our next steps. Lastly we acknowledge and thank Shire - now part of Takeda Pharmaceutical Company Limited - for their 2-years unrestricted grant, which has enabled the ESE team to deliver the PARAT programme of activities.

Jens Bollerslev

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Venue

The Duin & Kruidberg estate was first established in the 17th century as a summer residence for affluent residents of Amsterdam. Over the next three hundred years the estate was owned by a wide range of owners from His Royal Highness the Prince of Orange, to the ABN-Amro bank.

Over that time, the estate, house and gardens have undergone numerous adaptations, including one original house being demolished by the Cremer family in the early 20th Century to make way for this English styled country house you see today. In 1961, the Cremer's heirs sold the estate to the Dutch Trading Company who set it up as a holiday resort for their employees to enjoy, before it transformed into a hotel and conferencing venue for visitors to appreciate its grandeur and natural tranquillity again.





Speaker: **Camilla Schalin-Jääntti**
Finland

KEY MESSAGES:

- **Doctors need to distinguish between sporadic and familial forms**
- **Biochemical cure is less likely in familial primary hyperparathyroidism**
- **There are no data yet on conservative treatment**

Inherited Forms of Primary Hyperparathyroidism (MEN1,2,4, HPT-JT and FIHP): Diagnosis and Management

Assoc. Prof. Schalin-Jääntti presented a talk on diagnosis and management of inherited forms of primary hyperparathyroidism (PHPT). Sporadic disease accounts for 90-98% of PHPT cases. Familial forms are uncommon and therefore less easy to recognise (DeLellis, 2018). With familial primary hyperparathyroidism (FPHPT), seen in 2-10% of PHPT cases, the problem is germline mutation.

FPHPT can be divided into syndromic forms (MEN 1, 2 and 4; hyperparathyroidism jaw tumour syndrome [HPT-JT]) and non-syndromic familial forms, where hyperparathyroidism alone runs in the family (familial isolated primary hyperparathyroidism [FIHP]).

How to distinguish between sporadic and familial disease? If familial disease is recognised then the underlying mutation should be identified because this has implications for the family members. Affected and non-affected mutation carriers, need tailored follow-up, while those not carrying the mutation do not.

Characteristics of FPHPT

Familial forms should be suspected if patients have multigland disease or if there is early-onset (under 40 years) PHPT. Familial disease is more often recurrent and there is a higher risk of parathyroid carcinoma.

Part of the workup for suspected FPHPT is to take a detailed family history. Serum calcium measurements of family members can be performed plus other detailed clinical and biochemical, imaging and genetic workup. Genetic testing is recommended in order to identify the underlying mutation.

A retrospective study investigated the probability of positive genetic testing results in patients with a family history of PHPT (Lakis, 2018). The study comprised 657 patients and of these 60% had an underlying mutation: 91 MEN1, 14 CDC73 and 8 GCM2 mutations.

Patients with a family history of PHPT were younger: 55% of those with familial disease were under 45 years at diagnosis. There were more males with familial disease. Multigland disease was more common in familial HPT (70% vs 14%); there were a few cases of parathyroid carcinoma in familial PHPT, but none among patients with sporadic forms; and biochemical cure was less likely in familial forms (89% vs 96%).

Genetic studies

An example of a gene panel test for panel test for FPHPT includes testing for MEN1, MEN2 (RET) and MEN4 (CDKN1B), HPT-JT (CDC73 mutations), FHH 1-3 (CaSR, GNA11 and AP2S1), and GCM2 mutations.

Syndromic forms of PHPT

The syndromic forms are multiple endocrine neoplasia (MEN) 1, 2 and 4 and HPT-JT. With these syndromic forms, patients may have other tumours and other manifestations. For instance, patients with MEN1 may develop pancreatic tumours, lipomas and adrenal cortical tumours.

More than 60 germline mutations of CDC73 have been reported. It is a tumour suppressor gene, i.e. the protein that this gene encodes for, parafibromin, may thus be absent in the parathyroids. All patients who have such a mutation have a higher risk of developing tumours. Often this mutation leads to HPT-JT syndrome, but some families only have FIHP (though perhaps their tumours have not yet become manifest). CDC73 mutations are associated with parathyroid carcinoma. The HPT-JT syndrome may include ossifying jaw fibromas, and kidney, uterine, testicular and pancreatic tumours.

In FIHP, GCM2 and CDC73 mutations have been observed. GCM2 encodes a transcription factor which is expressed almost solely in the parathyroid glands. This factor is required for normal parathyroid development during embryogenesis. FIHP associated with germline GCM2 mutations is more aggressive and has a lesser rate of biochemical cure. Multigland disease is seen more frequently in patients with the mutation compared to those with sporadic disease.

Treatment of FPHPT

Symptoms, biochemistry (serum calcium, PTH etc) and 24-hour urinary calcium should be evaluated. Kidney stones and nephrocalcinosis should be sought, and bone densitometry and fractures investigated in order to best evaluate correct timing of surgery. Before surgery, it is recommended to perform sestamibi scintigraphy combined with SPECT/CT and a neck ultrasound because sometimes this discovers an abnormal ectopic gland. Total parathyroidectomy followed by autotransplantation is more common than subtotal resection. It is possible to treat some patients conservatively with cinacalcet, zoledronic acid or denosumab but as yet there are no data on the outcome of conservative treatment.



Speaker: **Ghada El-Hajj Fuleihan**
Lebanon

KEY MESSAGES:

- **FHH is a mild disease with no end organ damage**
- **FHH and mild hyperparathyroidism have overlapping clinical and biochemical features**
- **Pregnant women with FHH should be identified to monitor their newborns for hypocalcemia at birth**
- **Cinacalcet is FDA approved for all types of hyperparathyroidism but not FHH**
- **The place of drugs to reset abnormalities in calcium sensing in FHH and ADH is uncertain**
- **The best known calcilytic is ronacalret, the others are being tested in trials**

CaSR-mutations (FHH – ADH): Genetic and Clinical Perspective

Prof. Ghada El-Hajj Fuleihan discussed familial hypocalciuric hypercalcemia (FHH) and autosomal dominant hypocalcemia (ADH), genetic disorders of the calcium-sensing receptor (CaSR).

Experiments in the 1980s investigated the inverse sigmoidal relationship between PTH release and calcium. The CaSR receptor was cloned in the early 1990s by Edward Brown. Decreasing sensitivity of the receptor to calcium causes the syndrome of FHH, increasing sensitivity causes the syndrome of ADH.

Characteristics of FHH

Disorders of calcium sensing may be genetic, autoimmune, tissue-specific or induced by drugs such as lithium (Haden, 1997). FHH is characterized by mild to moderate hypercalcemia associated with levels of PTH and urinary calcium that appear inappropriate. For any given serum calcium, PTH levels are higher in FHH than normal individuals.

The hypercalcemic syndromes

Three distinct FHH syndromes have been characterised: FHH1 accounts for 65% of cases due to inactivating mutations in the CaSR itself, FHH2 (inactivating mutations in GNA11 down the signal transduction pathway of the receptor) and FHH3 (inactivating mutations in AP2S1 downstream the signal transduction pathway (Hannan, 2016). In neonatal severe hyperparathyroidism (NSHPT) patients inherit abnormal receptors from both parents.

Patients with FHH1 are mostly asymptomatic but they may have a family history (Hannan, 2018). FHH2 is mainly asymptomatic whereas FHH3 is symptomatic with more severe hypercalcemia, higher PTH levels and low bone mineral density in some patients, and cognitive defects in the children. NSHPT is clinically manifest at birth with severe hyperparathyroidism, severe bone disease and respiratory failure.

Differentiation of syndromes

It is not possible to differentiate between hyperparathyroidism and FHH using total calcium and PTH levels alone since values can overlap. The family history is essential in the differential diagnosis of the two. The overlap was illustrated in a study that measured calcium to creatinine clearance ratio (CCCR) in normal controls, FHH family members, and patients with hyperparathyroidism (Heath, 2001). The classical cut-off has been defined as less than 0.01 for FHH and more than 0.02 for hyperparathyroidism. Another paper found that of 1,000 patients with PHPT, most had a CCCR between 0.01 and 0.02 (Moore, 2018).

ADH

Autosomal dominant hypocalcemia is the mirror image of FHH. It is characterised by variable degrees of hypocalcemia with an inappropriately low PTH level for the calcium level. There is persistently elevated calciuria, suggestive of oversensitivity to serum calcium. The manifestations are variable degrees of hypocalcemia, ectopic calcification including basal ganglia, kidney stones and renal failure (Hannan, 2018). Similarly, the genetic defects are the mirror image of those in FHH.

Medical therapy

Since FHH is usually asymptomatic, treatment is not necessary. Total parathyroidectomy is beneficial in NSHPT. Pregnant women with FHH should be identified because high maternal calcium will cross the placenta and will inhibit endogenous PTH secretion in the fetus. For ADH in asymptomatic and mildly symptomatic patients, treatment may be unnecessary and should be given cautiously. Chronic hypocalcemia in children should be avoided. Calcium, vitamin D, exogenous PTH and thiazides are possible treatments. Careful monitoring of urinary calcium and regular kidney ultrasound are required.

Calcimimetics and calcilytics

On the horizon are drugs that reset the abnormalities in calcium sensing. In FHH, drugs that enhance or overcome the insensitive calcium receptor, calcimimetics, might be helpful; conversely, with ADH, drugs that reduce the oversensitive receptor, the calcilytics, might be helpful. To-date calcimimetic and calcilytic are not FDA approved for use in FHH nor ADH. The calcimimetics include tecalcet, cinacalcet and etelcalcitide. Examples of the calcilytics are NSP 2143 and encalaret (Hannan, 2018). Cinacalcet has been reported to work in most forms of FHH, lowering serum calcium and PTH levels and improving hypercalcemic symptoms. Most studies of calcilytics in ADH are in mouse models, and show increased serum calcium and PTH, and reduced urinary calcium excretion.



Speaker: **Lars Rejnmark**
Denmark

KEY MESSAGES:

- **PHP has to be distinguished from SHPT**
- **The characteristic phenotype is not always present**
- **Patients are at increased risk of cataract, cognitive impairment and infections**

PTH-receptor Mutations (PseudoHypoPT, Acrodysostosis)

Prof. Rejnmark spoke about mutations in the PTH receptor, including pseudohypoparathyroidism (PHP) and related disorders. He referred delegates to the first international consensus statement on these disorders, published in 2018 (Mantovani, 2018). This group of disorders is caused by different and complex genetic and epigenetic defects. PHP is the most common (types 1A, 1B, 1C and 2). These disorders also include pseudopseudohypoparathyroidism (PPHP), acrodysostosis and progressive osseous heteroplasia (POH).

PHP

PHP is characterised by resistance to the action of hormones acting through the G-protein coupled receptor (encoded by the *GNAS* gene)—PTH, TSH, gonadotropins and GHRH. The hallmark of PHP is PTH resistance, causing hypocalcemia with high PTH levels. These patients are also characterised by hyperphosphataemia and they may have other hormonal disturbances such as high TSH levels and GH deficiency. They may have a characteristic phenotype: physical findings including brachydactyly etc, short stature, macrocephaly, ectopic ossifications and early-onset obesity. Many also have neurocognitive impairment.

Ectopic ossifications are a characteristic of type 1A PHP as well as PPHP. They can be removed surgically if necessary. These patients are also likely to develop ectopic calcifications, due to alterations in calcium and phosphate levels within tissues. These calcifications are mainly present in the brain, predominantly in the basal ganglia and other brain areas, and can also cause cataract.

Treatment

Patients should be treated with activated vitamin D and calcium supplements, plus correction of other hormone abnormalities, and serum calcium and serum phosphate should be kept within the normal range while avoiding hypercalciuria. Serum PTH levels should not be suppressed: they should be kept in the upper part of the normal range or maybe even slightly above the upper limit of the reference range because sensitivity to PTH is often maintained in the distal convoluted tubule.

Monitoring these patients

Monitoring of biochemistry should include PTH, calcium, phosphate and creatinine measurements. Renal imaging should be performed at diagnosis to identify nephrocalcinosis or nephrolithiasis. Brain CT can be performed if neurological manifestations are present; ophthalmological examination should be performed to look for cataract; and dental examinations should be performed at regular intervals. Thyroid function should be tested once a year.

In these patients bone loss may occur as a result of elevated PTH levels, untreated hypogonadism or GH deficiency. Often these patients have relative resistance to PTH in their bone although overt manifestations are rarely seen. A cross-sectional study a couple of years ago compared 31 patients with PHP type 1A and 62 patients with non-surgical hypoparathyroidism (ns-HypoPT) (Underbjerg, 2018). Those with PHP were more frequently being treated with thyroid hormone supplements. PTH levels were much higher in PHP patients, and TSH levels were also higher. PHP patients had lower 24-hour urinary calcium compared to the ns-HypoPT group.

Looking at bone turnover markers, similar results were observed in both groups with levels in the lower part of the age- and sex-specific reference intervals. In the group of patients with PHP there was a significant correlation between PTH levels and bone turnover markers, indicating that these patients do not have complete resistance to PTH in bone.

HR-CT scans, to look at volumetric BMD and bone architecture in this group of patients, showed that they had lower total and trabecular vBMD than patients with non-surgical HypoPT while the cortical values did not differ between the groups. This suggests that chronically elevated PTH affects bone differently in PHP and PHPT.

Co-morbidities

Co-morbidities in patients with PHP have been compared to the general population (Underbjerg, 2016). Patients with PHP are more likely to develop cataracts and neuropsychiatric disorders as well as infections. They are less likely to develop renal diseases than those with nonsurgical hypoparathyroidism, however.

In summary, PHP can be confused with secondary hyperparathyroidism (SHPT). It has a clinical phenotype but this is not always present. PTH resistance does not seem to be complete in bone or in kidney. These patients are at increased risk of cataract, neuropsychiatric disorders and infections but they are not at increased risk of renal diseases or fractures.



Breakout discussion conclusions

Research

- We need more long-term data on normocalcemic hyperparathyroidism: should we treat it surgically or not?
- We want long-term data on treatment with PTH in hypoparathyroidism
- We want specific clinical data and ideas from biopsying tissue and blood material. Perhaps we could do molecular testing of tumours to identify which mutations are present
- The diagnostic workup to distinguish between primary hyperparathyroidism and familial hypercalcemic hypocalciuria (FHH) needs to be improved
- We should start registration of FHH patients
- Why do hypophosphatemic patients develop hyperparathyroidism? There is no good pathophysiological explanation
- Does the presence of vascular and other calcifications (especially in pseudohypoparathyroidism) relate to outcomes? Long-term follow-up is needed
- Why do patients with hypoparathyroidism have more infections?
- How do we diagnose more patients with familial forms of hyperparathyroidism? We do not seem to have many well characterised large families with transmission of a putative mutation with a phenotype; PARAT could look at how to aid the identification of the range of genes which give rise to familial hyperparathyroidism
- We should develop a standardised procedure to decide which patients will go for more advanced and sophisticated diagnostic workups. Maybe we should develop a risk score
- When the clinician sees an affected patient with a big family, go for whole genome sequencing to identify potential new mutations. We are not doing enough to obtain DNA samples from all the family members, those affected and unaffected
- Why do some patients with familial hyperparathyroidism and single-gland disease not develop four-gland disease, or develop four-gland disease in sequence over the course of many years?
- What about the non-classical manifestations of patients with so-called normocalcemic hyperparathyroidism. Is hyperphosphatemia more sensible than calcium in predicting the development of primary hyperparathyroidism? If it is reversible, what is the mechanism?
- The calcium-sensing receptor's extracellular domain has binding sites for phosphate. It is interesting to think that one receptor detects the overall calcium-phosphate product and that this regulates the circulating PTH level. But studies to prove that would be challenging to do

Management

- How should the practising endocrinologist enquire about a patient's family history to pick up these familial forms of PHPT in the clinic? Should he ask the primary care physician to do serum calcium measurements on these family members?
- If the clinician performs gene panel analyses and the patient comes back as mutation-negative, what kind of follow-up is required?
- Only about two thirds of patients with FHH turn out to have a mutation in one of the genes, and the question is what to do about the ones who are mutation-negative. One approach is to follow them up in your clinic and not to send them to the surgeon unless there is some evidence of target organ damage
- ADH should not be treated simply as a genetic diagnosis. There is no cutoff clinically to distinguish ADH from hypoparathyroidism: if a patient with hypoparathyroidism has not had surgery and there is no obvious cause then he should be tested for ADH with gene analysis

- Pseudohypoparathyroidism is challenging to diagnose in clinical practice, and to distinguish from secondary hyperparathyroidism
- These patients sometimes become hypercalcemic over time: what should be done about follow-up of these individuals and how do you prevent this occurring? The solution to many of these questions would be answered by a Europe-wide database registry to follow patients and their family members
- In hyperparathyroidism, there is a lot of work that needs to be done in challenging the diagnostic odyssey that patients currently face, looking at the tools that we have available to us to make a diagnosis, and when to deploy genomics into standard practice
- We do not yet know what we are doing in the treatment of normocalcemic PHPT
- Is the "benign" condition of FHH really benign, and how should these patient be followed up? What is the prognosis and how should those really rare cases with nephrolithiasis be managed?
- Many people don't really understand hypoparathyroid disorders, so it is really important to raise awareness about them
- We should perhaps be thinking about classification not in traditional descriptive terms but using appropriate molecular classification of the diseases in our area
- We need some designated specialist centres for bone and calcium metabolism across Europe
- Relying on sestamibi is already outdated, so alternative imaging modalities need to be investigated

Education

- Focus on university medical school curriculum, GP specialists, endocrine colleagues, patients and encouraging patient organisations to use ESE published materials for this purpose
- Ambassadors can spread education through guidelines and consensus
- An extended version of this meeting could be held at the ECE congress, with webinars and interactive seminars
- The PARAT ambassadors should formulate a simple page of information for GPs about hypo- and hypercalcemia as they often overlook changes in serum calcium
- Create brief slides sets in English we can all use in our clinical settings, that can be used by GPs and specialists
- We should question the misconception that parathyroid surgery is an easy procedure so every surgeon should be able to perform it
- Endocrinologists also need the education and awareness to detect and diagnose these rare conditions
- Guidelines should emphasise that parathyroid surgery is done in a multidisciplinary way, with both pre- and post-surgical interventions
- Identify clinical scenarios where education would be helpful. One is the scenario where you are making the differential diagnosis between FHH and PHPT. Some patients are not diagnosed until after surgery
- We should teach surgeons that if you identify the four parathyroid glands and the patient continues to be hypercalcemic, there is a less than 3% chance that he has a fifth gland but it is highly likely that he has FHH
- These disorders have a low prevalence and it is easy to miss the differential diagnosis, and this in some cases may lead to overtesting
- How should we educate patients with inherited forms of parathyroid disease about the importance of testing their children and also make their children more aware they may need to be tested?
- Maybe a complementary education strategy to patient information leaflets would be to organise seminars for patients with rare diseases



Speaker: **Bart L. Clarke**
USA

KEY MESSAGES:

- There is little evidence and there are few trial data
- There are no evidence-based guidelines to date for either hypoparathyroidism or hyperparathyroidism during pregnancy or lactation
- Hypoparathyroidism and hyperparathyroidism are high-risk obstetric states

Management of Hypoparathyroidism during Pregnancy

Prof. Bart L. Clarke gave an overview of parathyroid disorders in pregnancy.

Chronic hypoparathyroidism in pregnancy and lactation

It is probably reasonable to apply the 2015 ESE guidelines for management of chronic hypoparathyroidism (Bollerslev, 2015) to pregnant and lactating women.

Various changes that occur during pregnancy affect parathyroid hormone and calcium and related mineral metabolism (Khan, 2019). The placenta makes PTHrP: this is the main driver of bone resorption during pregnancy but it also affects the synthesis of 1,25 (OH) vitamin D by the kidneys, in turn stimulating intestinal calcium absorption. During lactation the skeleton becomes the major source of calcium. The pituitary also interacts with breast physiology to drive lactation.

Management

This is a high-risk obstetric state, so optimal care is likely going to involve a team of people.

Serum 1,25-dihydroxyvitamin D levels increase 2-5 fold during pregnancy in patients with chronic hypoparathyroidism. The renal filtered load increases for calcium, resulting in hypercalciuria and sometimes kidney stones.

Maternal hypercalcemia suppresses fetal parathyroid gland development and postpartum crises can occur because the baby cannot make PTH. By the same token, hypocalcemia in the mother can lead to fetal and neonatal secondary hyperparathyroidism. Fetal secondary hyperparathyroidism may cause undermineralisation of the skeleton, and fractures have been reported to occur in utero or during delivery. Additionally, inadequate treatment can lead to premature contractions and miscarriage.

Maintaining a low-normal serum calcium in the mother is reasonable, making appropriate adjustments to calcium, calcitriol and vitamin D2 and D3 doses to get them into the desired range. PTH analogues have not been evaluated in pregnancy. If hypoparathyroidism is well managed then good maternal and fetal outcomes are to be expected.

There are many changes in normal calcium physiology during pregnancy and lactation (Kovacs, 2011). During lactation there is a high demand for breast milk calcium; a nursing healthy baby will take 210-1,000 mg daily.

Transient increases in calcium and calcitriol requirements may occur for several days after the baby is born.

Primary hyperparathyroidism in pregnancy and lactation

PTH levels generally decrease by 70% in the first trimester and gradually increase to the mid-normal range by the third trimester. It is therefore harder to diagnose PHPT in a pregnant woman. There is a 2% risk of stillbirth and neonatal death and a 15% risk of neonatal tetany even in the modern era.

Surgery for primary hyperparathyroidism can be carried out during pregnancy but is done in less than 1% of cases, and generally during the second trimester because it is less likely to precipitate early delivery. Medical management options are limited. Patients who have asymptomatic primary hyperparathyroidism may just be observed throughout the pregnancy. Milder cases that are diagnosed in the third trimester usually can wait for surgery until after delivery. Rapid and severe worsening of postpartum hypercalcemia may occur in the mother once the placenta has been delivered.

Medical management during pregnancy is limited to hydration, and correction of electrolyte abnormalities. Thiazides are not used in PHPT, but may be used in non-pregnant or non-lactating women with HypoPT. Bisphosphonates are relatively contraindicated because of the potential for side effects in the baby. Denosumab is not recommended in humans. High-dose magnesium is a potential option but has not yet been studied. Cinacalcet has been tried but is a high-risk option. Patients that are followed medically should be offered parathyroidectomy as soon as the baby is born.

Primary hyperparathyroidism typically worsens if parathyroidectomy is not carried out after parturition, partly due to the placental calcium loss. Medical options are limited during lactation because no agents are approved.

Surgery is the best option after parturition. Serum calcium needs to be monitored closely during lactation if surgery is not to be carried out. There are no other medical options in the literature, so one option that would help these mothers is to stop lactation as soon as possible.

In summary, there are no evidence-based guidelines to date for either hypoparathyroidism or hyperparathyroidism during pregnancy or lactation.



Speaker: **Jens Bollerslev**
Norway

KEY MESSAGES:

- It is unknown whether current combination treatment regimens normalise bone metabolism
- Vertebral fractures are relatively common in idiopathic HypoPT
- Most patients develop HypoPT after neck surgery, against a background of normal bone mass and strength

Bone Metabolism and Fractures in Chronic Hypoparathyroidism in Adults

Prof. Jens Bollerslev spoke about bone metabolism and fractures in chronic hypoparathyroidism (HypoPT). Most patients with HypoPT develop the condition in adulthood following neck surgery. There are two hormones in play here, PTH and 1,25 dihydroxy vitamin D. Standard treatment does not restore normal physiology, and that is of potential importance for the long-term biomechanical properties of bone.

Bone modelling occurs during growth and then trabecular and cortical remodelling take place in adulthood (Henriksen, 2011). The remodelling in adulthood is stochastic, dedicated to calcium homeostasis and under hormonal control, but it is also targeted in order to remove the microdamage that goes on in bone all the time. Stochastic remodelling refers to a type of homeostasis maintained by the hormones, PTH and Vitamin D being most important. These are the hormones that are lacking in HypoPT.

Histomorphometry studies

Langdahl's 1996 paper (Langdahl, 1996) compared the histomorphometry of conventionally treated HypoPT with normal controls. In patients with HypoPT, who were at that time under treatment with calcium and vitamin D, the different phases in bone remodelling were increased in time with a slight, non-significant positive balance. Thus, although HypoPT is a low turnover state all phases of bone remodelling were increased in time, but the balance seemed to be preserved.

A newer study from Columbia University, NY (Rubin, 2008) illustrates exactly the same: trabecular bone volume is increased, the cortical thickness or width of bones is increased, the whole core of the bone is increased and the thickness of the single trabecula is increased. That results in dense bone in patients with hypoparathyroidism.

Fracture risk

Will this dense bone fracture? In one study, more than 1,800 patients with possible post-surgical HypoPT were identified but there was no increase in fracture rate (Underbjerg, 2018).

Idiopathic HypoPT (IH) refers to HypoPT that mostly develops in childhood before the closure of the growth plates. Chawla (Chawla, 2017) studied vertebral fractures in 104 patients with IH versus 64 controls. There was a clear increase in vertebral fractures in IH patients, with at least one vertebral fracture in 18.3% of patients versus 4.7% of controls. Most of these fractures were low-grade fractures.

PTH replacement

What happens when the PTH is reinstated? Sikjaer (Sikjaer, 2011) published a study of bone metabolism when PTH (1-84) or placebo was added to conventional treatment with calcium and vitamin D analogues for 24 weeks. The bone turnover was increased with PTH, and the BMD of the whole body, hip and spine decreased. This is to be expected: as when remodelling begins the bone remodelling space increases, thereby decreasing the bone density.

A recent study of the long-term effects of PTH (1-84) substitution therapy in HypoPT (Rubin 2018) followed 13 patients (and compared with 45 controls at baseline) using histomorphometry. The study showed that indices of bone remodelling increased with long-term treatment. The cohort of patients followed for a mean duration of 8 years were a mixed population regarding aetiology, almost half and half idiopathic and post-surgical HypoPT. At baseline the mean age was 44.7 years and they had had their disease for 14 years. It is discussed in the paper that the indices of bone remodelling increase rapidly in all envelopes following initiation of treatment with PTH. Some of the indices even exceeded normal values. A new steady state seemed to be established, not necessarily at the physiological level.

Conclusions

HypoPT is complicated from an endocrine perspective. It is based on a heterogeneous group of disorders with different aspects and consequences for bone metabolism and for the mechanical properties of bone. Standard treatment does not normalise bone remodelling. Substitution therapy increases bone remodelling, presumably reaching a new steady state although that is not certain. The consequences for bone of the background disease and also the timing of its development are unknown. The effects of the different algorithms on bone metabolism need to be ascertained, and the importance of extraskeletal effects of disease and treatment for bone metabolism and strength are as yet unknown.



Speaker: **Antonio Sitges-Serra**
Spain

How to Avoid Surgical Damage to the Parathyroid Glands

Part I: Current Best Practice

Prof. Sitges-Serra discussed in situ preservation of the parathyroid glands during total thyroidectomy.

Some of the main risk factors for postoperative hypoparathyroidism cannot be modified, including the need for lymph node dissection, age and female gender. Hence the modifiable risk factors appear to be avoiding autotransplantation and avoiding inadvertent parathyroid gland resection.

The prevalence of hypoparathyroidism after accidental resection of one or two parathyroid glands is somewhere between 5 and 15%.

KEY MESSAGES:

- **Calculating the PGRIS score gives the likelihood of recovery. Patients should be given enough calcium and calcitriol to avoid hypocalcemia in the days following surgery**
- **After accidental resection of a parathyroid gland hypoparathyroidism occurs in 5–15% of patients**
- **Some risk factors cannot be modified such as age, gender or the need for lymphadenectomy**

The PGRIS score

The PGRIS score, the number of parathyroid glands left in situ, can be calculated by subtracting from 4 the number of glands implanted in the sternocleidomastoid muscle or accidentally resected. The more parathyroid glands are preserved in situ, the fewer problems the patients have (Lorente-Poch 2011). There is a progressive worsening of parathyroid function as the number of parathyroid glands in situ falls.

Parathyroid gland autotransplantation is not the answer, however. Lorente-Poch and colleagues performed a study which looked at more than 650 total thyroidectomy patients (Lorente-Poch 2017). They found that autotransplantation does not improve the long-term results.

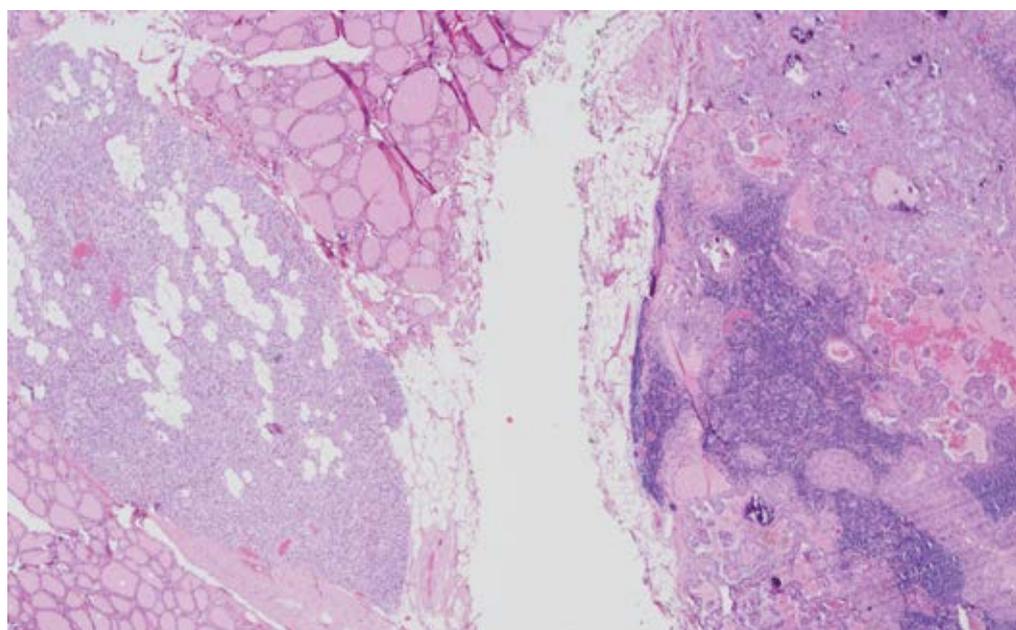
Advantages of leaving parathyroid glands in situ

Leaving parathyroid glands in situ has tremendous advantages in terms of recovery. If four parathyroid glands remain in situ then a 90–98% recovery rate of postoperative hypocalcemia may be anticipated, some of these patients improving after a year. However, if only 1, 2 or 3 glands are left in situ the recovery rate is about 60–70% and there is no further improvement after 1 year.

The term parathyroid splinting describes intensive medical treatment of hypocalcemia after thyroid surgery (Villarroya-Marquina 2018). If the serum calcium is kept in the upper normal range, this rests the injured or ischemic parathyroid glands and allows for better recovery. A nomogram has been developed: by determining at 1 month the serum calcium and iPTH, it is possible to calculate the chance of recovery at 1 year.

The PDS score

A very simple intraoperative score, the parathyroid damage score (PDS), has been devised in order to describe how the surgeon handles the parathyroid glands during surgery and how the parathyroid glands function. For each parathyroid gland the score is 0 for no mobilisation, 1 for minimal dissection and 2 for substantial dissection. The scores are added to give the PDS. Those patients with a PDS of 0–3 have a 19% chance of postoperative parathyroid gland failure; by contrast a PDS >5 results in an 80% chance of PG failure. There is a close correlation is between biochemical data and how much the parathyroid glands are handled.



Inadvertent parathyroidectomy in a case of an intrathyroidal parathyroid gland adherent to a metastatic lymph node (papillary carcinoma). With permission of author.



Speaker: **Lars Rolighed**
Denmark

How to Avoid Surgical Damage to the Parathyroid Glands

Part II: Prospective Techniques

Dr Lars Rolighed discussed future perspectives in protecting the parathyroid glands during thyroidectomy, focusing on fluorescence. A specific light source is directed at tissues with some sort of fluorescent ability and then the fluorescence is detected by specialised cameras. The parathyroid gland has an autofluorescent capacity: a study by McWade (McWade, 2013) showed that the fluorescence intensity is markedly different from thyroid tissue at specific wavelengths. This technique can be used intraoperatively to distinguish between thyroid and parathyroid tissue.

Many new devices have been made. In addition there are new techniques which now have overlaid images (McWade, 2014) to visualise the parathyroids.

A recent study (Benmiloud, 2018) investigated whether fluorescence could help parathyroid identification during thyroidectomy. The study involved two surgeons who carried out total thyroidectomies over two time periods, the first period 12 months in length and the second period 8 months. In the first period there was a 16-21% postoperative hypocalcemia rate for both surgeons. In the second period one surgeon used autofluorescence; the rate of postoperative hypocalcemia was reduced to 5% among these patients.

In May 2019, a surgical team in Argentina published the first randomised trial with autofluorescence (Dip, 2019). In this trial 170 patients were randomised to total thyroidectomy with normal white light or with near-infrared autofluorescence. In the white light group, 11.8% of patients had very low postoperative calcium (<7.6 mg/dl), compared to 1.2% with very low calcium in the autofluorescence group.

New developments include the PTeye based on autofluorescence, which identifies 96% of parathyroid glands. It is simply a device that can be put on the thyroid and the parathyroid; it is now FDA approved but there are no large studies as yet. Another system from Stryker is called the SPY-PHI system. This is a hand-held device that contains a camera. It needs to be used together with indocyanine green (ICG), a green dye given intravenously.

A randomised trial using this technique was recently published in the British Journal of Surgery (Vidal Fortuny, 2018). The trial included 146 total thyroidectomy patients who had at least one well vascularised parathyroid gland left. The authors stated that ICG angiography reliably predicts vascularisation of the parathyroid glands and obviates the need for postoperative measurement of calcium and PTH and supplementation with calcium in patients with a well vascularised parathyroid gland.

KEY MESSAGES:

- **This new approach can help surgeons find and preserve the gland and vascular supply**
- **Is parathyroid monitoring as important as nerve monitoring?**
- **Should the technique be used in both bilateral and unilateral cases?**
- **We need better comparisons across products**



Breakout discussion conclusions

Research

Pregnancy

- There is a lack of data on parathyroid disease in pregnancy. We should start prospective registration of patients in order to see what the best treatment modality is, and how their treatment approaches relate to maternal outcome and outcome for the child
- What are optimal 1,25 dihydroxy vitamin D, and the optimal vitamin D doses in pregnancy?
- Young women have 2–4 times the PHPT risk compared to males and even compared to older females after adjustment for other risk factors
- What cut-offs for surgery of PHPT should be used in this setting and is using sestamibi imaging dangerous in pregnant women?
- It would be interesting to do studies, probably using ultrasound, in pregnant women to see whether the parathyroids get larger during pregnancy and then regress afterwards

Bone disease

- We need more data on the long-term outcomes of PTH treatment because it is not a physiologic replacement of PTH. There are signs of concern regarding the long-term outcomes
- Stochastic remodelling in hypoparathyroidism may be driven by locally produced IGF-1 or some other regulatory factor, more than by systemic factors.
- Kidney failure is also a limiting factor for increasing BMD
- In mice with hypothyroidism, there is a regulation of the Wnt signalling pathway in bone. Could this be relevant in humans? What does drive peak bone mass?

Surgery

- We need more data from controlled randomised trials to prove the new approach with fluorescent light
- Does this technique improve outcomes for surgeons?
- How is the outcome related to the experience of the surgeon? The European Society of Endocrine Surgeons (ESES) recommend a minimum of 40 thyroidectomies per surgeon per year
- The indication of total thyroidectomy for benign disease should be carefully balanced

Management

Pregnancy

- We should consider developing an expert consensus statement on pregnancy in patients with parathyroid disease, in collaboration with obstetric colleagues. Some current practices are probably not appropriate
- A joined up position statement would be informative to healthcare professionals and patients. Patients themselves can then assess who they should be seeing and the kind of skills and experience that these professionals should have
- The multidisciplinary team is crucial. It will need to be flexible to manage these patients with complex problems. These might include patients with psychiatric problems
- We need to care for both the mother and child from booking in the antenatal period to the postpartum period
- Focus on the fetus
- Pregnancy is a high-risk state and delivery is high-risk in these patients. Pregnant women will need more frequent blood sampling, and the baby will need urgent blood sampling

- Patients should be informed that risk is increased
- Develop cut-offs for both hyper and hypoparathyroidism in pregnancy; that might be something the society could help with by developing or stimulating new registries, bringing people together who have access to these data
- The new mother should stop breastfeeding in the event of a fracture

Bone disease

- We should not rely only on DEXA test results, which can provide inappropriate reassurance
- Delegates recommended against BMD testing, which is not indicated universally and which some consider useless. Management needs to be individualised if there are signs or symptoms
- Should clinicians screen for fracture in patients with parathyroid disease?
- Given the lack of fracture outcome data, could the PARADIGM registry (if large enough and long enough) offer any insight into potential roles of PTH therapy and fracture risk?
- We need to use more innovative technologies such as bone biopsy
- In older patients with hypoparathyroidism who fracture, what is the interface between age-related increase in fracture risk and hypoparathyroidism? It is uncertain how to manage such patients

Surgery

- A DEXA scan may not be the right way to assess fracture risk after surgery. We need a different type of evaluation
- We need to centralise care so that surgeons have good, high-volume experience
- The issue of whether to do total or subtotal thyroidectomies should be debated to reduce the risk of having more patients with postoperative hypoparathyroidism. There are international variations in threshold for total thyroidectomy
- We need consensus about appropriate practice and the relative use of radioiodine and thyroidectomy
- Clinicians should continue to measure calcium values, even if they are controlled immediately after surgery
- This may present an opportunity to set up a registry, which could eventually provide information for patients
- We need to ensure that new techniques and methodologies have been properly tested before they are introduced into clinical practice
- It might be useful to collaborate with the EUROCRINE register to include new parameters relevant for new studies
- Technology could help overcome international variabilities in threshold for total thyroidectomy and could improve cost-effectiveness of treatments



Education

Pregnancy

- Pre-pregnancy counselling is necessary, similar to that given for diabetes and many other conditions. Awareness is an issue
- We should differentiate between patients with pre-existing disease or patients diagnosed during pregnancy, mostly patients with PHPT
- For patients diagnosed during pregnancy, management should probably be symptom-oriented. Otherwise, clinicians need to decide who should do investigations such as calcium and albumin measurements, and how often
- If pregnant women do not want parathyroid surgery, they can be reassured that it is a relatively small procedure
- For patients with previously recognised disease, endocrinologists should be advised to monitor the parameters and adjust treatment more frequently than usual, in collaboration with gynaecologists and neonatologists
- Patients should be advised to tell their endocrinologist if they become pregnant

Bone disease

- Potential new registries for rare diseases could be in collaboration with the Endo-ERN or a group of centres.
- On the subject of hypoparathyroidism, there is a distinction between patients with post-surgical disease and younger patients with congenital or idiopathic disease

- Bone disease can be a pertinent issue in younger patients
- Which modalities should be used in order to diagnose bone disease in younger patients? Should diagnosis be fracture-oriented?
- In transition between paediatric to adult endocrinologist, information should not get lost
- For post-surgical hypoparathyroidism, there is probably not enough evidence about the severity of bone disease or whether it translates into an increased fracture risk; or about the long-term effects of replacement therapy on fracture risk.
- How should osteoporosis be managed in patients with post-surgical hypoparathyroidism? It is counterintuitive to use bisphosphonates. Treating with PTH for two years does not make sense either.
- Awareness of bone metabolism in patients with parathyroid disease is low among our colleagues

Surgery

- Running specialised courses would be helpful to increase awareness of the risk of hypoparathyroidism after surgery
- It needs to be high-volume surgeons who do this surgery
- Evidence needs to be gathered for use of fluorescent techniques, and to find out how the results compare with those from experienced surgeons doing standard procedures at high volume
- There are political, financial, cultural and national challenges to establishing uniform surgical strategies



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Speaker: **Claudio Marcocci**
Italy

Atypical Parathyroid adenomas

Part I: Definitions and Characteristics

Clinical characteristics and management of atypical parathyroid adenomas (APA) were discussed by Prof. Claudio Marcocci. These are a group of parathyroid neoplasms of uncertain malignant potential.

Clinical and biochemical data were investigated in a large series of 355 patients. (Cetani, 2019) In this study the female to male ratio was 1.5, which is not typical among benign parathyroid tumors, and the mean age at diagnosis was 44 years. Bone involvement was observed in 18%, renal involvement in 29%, a palpable lesion in 15% and calcium and PTH levels were higher than those commonly found in benign forms of primary hyperparathyroidism. After surgery, confirmation or rejection of the diagnosis of APA or parathyroid carcinoma (PC) is relevant for further investigation and management.

Algorithm for assessment

An algorithm for the assessment of suspicious parathyroid lesions in patients with primary hyperparathyroidism was proposed by Shulte and Talat (Shulte/Talat, 2012). The clinician may make use of the 3+3 rule: if the serum calcium is above 3 mmol/L and the lesion size greater than 3 cm then this is quite suspicious. Also, if the patient has a positive family history and a mutation in the CDC73 gene these are further clues that the lesion may be cancerous.

Further investigations of suspicious lesions include ultrasound, PTH assays and molecular profiling. If the 3rd to 2nd generation PTH ratio is inverted parathyroid carcinoma is more likely. In the future, it may be possible to do some molecular profiling of blood.

The sensitivity and specificity of ultrasound features were compared in a study of 65 patients (Sidhu, 2011). The parathyroid lesions were greater than 1.5 cm: infiltration and calcification had a PPV of 100%, and suspicious vascularity a PPV of 75%.

When clinical, biochemical and instrumental findings raise the suspicion of malignancy a more extensive surgery (en-bloch resection), rather than a selected excision should be performed. Further testing after surgery may include CDC73 mutational analysis, and this can be of some help in predicting recurrence. There are discrepant results of the impact of parafibromin staining on outcome.

Surveillance after surgery

Some suggest close follow-up, even if the risk of recurrence is low, and independently of immunostaining results (Kumari, 2016). Others propose close follow-up only in atypical large tumours and/or loss of parafibromin staining.

Summary

Young age, male gender and a moderately severe clinical picture raise the suspicion of APA or PC. Ultrasound, PTH assay ratio and biomarkers are potentially useful preoperatively. In suspected cases, more extensive surgery is required. Mutational analysis is valuable because CDC73 mutations require extension of genetic testing to first-degree relatives and parafibromin staining should be performed on those tumours.

KEY MESSAGES:

- Presenting manifestations are not specific
- Differentiation between APA and PC is needed
- This affects patient management



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Speaker: **Hans Morreau**
The Netherlands

KEY MESSAGES:

- **The main challenge is to exclude parathyroid carcinoma**
- **Current biomarker profiles are of limited value in delineation**

Atypical Parathyroid adenomas

Part II: A diagnostic View

Prof. Hans Morreau offered a diagnostic view from a pathologist on these adenomas. Atypical parathyroid neoplasms may be called atypical parathyroid adenoma (APA) (Cetani, 2019), parathyroid adenomas of uncertain significance, or equivocal parathyroid carcinoma (PC). The latter term is of value because at least it recognises that there may be some doubt.

The diagnosis of APA is in theory quite simple. Unequivocal evidence of malignancy is lacking; atypical features in comparison to typical adenomas are present; at first diagnosis there is no capsular invasion or invasion of the capsular or pericapsular vessels or invasion of surrounding structures; and at follow-up no local recurrence or distant metastasis is found.

Histological features include pseudo capsular invasion, cellular pleomorphism, nuclear atypia, mitotic activity, thick fibrous bands and a trabecular growth pattern. Many biomarker studies have been performed: genetic markers include MEN1, CCND1 and CDC73. Data on chromosomal losses and gains, allelic losses, epigenetic alterations and miRNA profiles are so far not used in clinic, also because there is a huge overlap between the profiles of atypical adenomas and carcinomas.

As regards immunohistochemical (IHC) profiling, the tumour may be tested for Ki-67 and parafibromin. Galectin-3 and PGP9.5 are markers that can be used. It is stated in the literature that there is a low risk of recurrence if the tumour is parafibromin-positive and PGP9.5 and galectin-3 negative. Conversely, there is a higher risk of recurrence in parafibromin negative cases with somatic or germ line CDC73 DNA variations. The margins of surgical resection are important, maybe more important than the tumour's underlying biology, since already 90 to 95% of all parathyroid carcinomas are cured by adequate surgery as shown in Finland. It is not yet known whether APA are precursor lesions for carcinoma.

Remarkable casuistics

Cases initially diagnosed as APA but with local or distant metastasis during follow-up, either with or without CDC73 variations, were discussed. Also unusual oncocytic APA and PC cases were discussed with an unique chromosomal landscape with near haploidisation similar to what described for Hurthle cell malignancy of the thyroid (Corver et al 2014, Ganly 2018, Ganly 2018)

Conclusions

The main relevance of diagnosing APA is this: has parathyroid carcinoma really been excluded? The slight risk of local and distant recurrence should be discussed with the patient: if he or she has an atypical lesion or even parathyroid carcinoma in the absence of a somatic or germ line CDC73 pathogenic DNA variation and if parafibromin staining is positive then the chance of distal metastasis is far lower. Adequate surgical margins are of importance in preventing local recurrence.



Speaker: **Stefan Pilz**
Austria

KEY MESSAGES:

- There remain knowledge gaps in PTH regulation and measurement
- Assay standardisation is required
- There is a low evidence base for treatment

Secondary Hyperparathyroidism: Causes, Consequences and Non-surgical Management

Dr Stefan Pilz talked about the causes, consequences and non-surgical management of secondary hyperparathyroidism (SHPT), which is defined as an appropriate increase in PTH in response to a stimulus, in most cases low serum calcium. There is a very complex interplay in the regulation of PTH.

The genetic variants associated with circulating PTH were identified in a large genome wide association study (RobinsonCohen, 2017). SNPs from five independent regions were associated with serum PTH concentrations, including CYP24A1, a gene encoding the primary catabolic enzyme for vitamin D metabolites.

There is a great need to standardise measurement of PTH between different laboratories and different assays. There is also work to be done in establishing reference ranges for PTH.

Drivers for elevation of PTH

A long list of factors may increase PTH, including gastrointestinal causes of malabsorption, diet, vitamin D-related causes and kidney disease. The link between calcium and sodium is very interesting. There is crosstalk between these two fundamental systems. One study showed some very striking findings among patients with primary aldosteronism (Pilz, 2012). Many of these patients suffer from secondary hyperparathyroidism but when treated surgically or medically their PTH levels drop immediately. The mechanism is uncertain but the finding is important since many patients in the clinic have primary or secondary hyperaldosteronism.

The large variation in PTH levels that is seen in patients cannot be fully explained by current knowledge, and makes differential diagnosis difficult. More dynamic functional testing such as calcium suppression tests might help in this regard. Measurement of vitamin D status is also important.

Consequences of secondary hyperparathyroidism.

Those with a high PTH level have an increased risk for a variety of adverse outcomes, for fractures, cardiovascular mortality and so on. PTH receptors are expressed in the heart and there is a lot of evidence to show that PTH has direct effects on the cardiovascular system. Patients who have cardiovascular disease, but are not suffering from CKD or from primary hyperparathyroidism, have increased risk of adverse outcomes and mortality when PTH levels are high (Pilz 2010).

Treatment

The cause of the elevation of PTH should always be addressed but most valuable is vitamin D supplementation. A recent RCT (Bislev, 2019) in women with vitamin D deficiency and high PTH documented that vitamin D supplementation improved bone microstructure.

Dr Pilz briefly touched upon a recently published vitamin D supplementation study (Manson 2019). This was a randomised trial of vitamin D 2,000 IU per day and omega 3 FA 1g per day against placebo for prevention of cancer and cardiovascular disease among more than 25,000 members of the general US population. There was no significant effect regarding outcome, but the effects were evaluated in a patient group with almost optimal vitamin D levels. The question is whether it is a good approach to add vitamin D supplementation to a group with a high background level of vitamin D supplementation.

Treatment of SHPT in CKD

The new guidelines (KDIGO, 2017) acknowledge that the optimal level of PTH is not known but that patients whose PTH is rising or consistently elevated should be evaluated for modifiable factors such as vitamin D deficiency. The guidelines suggest that calcitriol and vitamin D analogs should not be routinely used for patients with CKD G3a-G5 and elevated PTH levels who are not on dialysis. For patients with CKD G5D, the guidelines suggest calcimimetics, calcitriol or vitamin D analogs, or a combination to treat hyperparathyroidism.

So what is the evidence behind these recommendations? There are good data from observational studies to show that active vitamin D analogs may be associated with improved survival in CKD but there are no randomised controlled trial data to confirm this. Results from the PRIMO trial of paricalcitol (Thadhani, 2012) were very disappointing: 48 weeks of therapy did not improve left ventricular mass index or measures of diastolic dysfunction in patients with CKD. The EVOLVE trial (EVOLVE, 2012) evaluated the effect of



Speaker: **Neil Gittoes**
UK

KEY MESSAGES:

- Awareness of PHPT in general practice is low
- PTH interpretation can be difficult
- It is unknown whether intervention affects outcome in those with mild disease

Primary Hyperparathyroidism – NICE Guidelines

Professor Neil Gittoes spoke about NICE guideline 132 on the diagnosis, assessment and initial management of primary hyperparathyroidism (PHPT) (NICE, 2019). The purpose of the guideline was primarily to increase awareness of PHPT, its symptoms and when to test for it. From the patient's point of view, the purpose was to reduce the delay in diagnosis. Finally, to provide some clear advice on when to offer surgery and what is the best type of surgery, and to produce peer advice on long-term management of such patients. Pregnancy in patients with PHPT was also covered.

Primary care issues

The awareness of PHPT is low in primary care. GPs are encouraged to make the link, to think about the underlying diagnosis and to measure the albumin-adjusted serum calcium if the patient has any of the classical symptoms that might indicate PHPT. The guidelines reinforce the link between PHPT and potential end-organ disease. They addressed the issue of normocalcemic PHPT, introducing a serum calcium towards the upper part of the normal reference range to try to capture the population of patients with normal calcium and PHPT.

PTH interpretation in primary care can be difficult. The emphasis of the guideline is really focused on safety. It is unwise not to check the PTH in a patient with raised calcium. Conversely, if the PTH is below the reference range then the patient should be referred and an alternative diagnosis should be sought.

Secondary care issues

The differential diagnosis of FHH needs to be excluded. After diagnosis of PHPT, patients should be assessed for symptoms and comorbidities using eGFR or serum creatinine, DXA scans and ultrasound of the renal tract.

Parathyroidectomy is known to be effective in reducing complications in people with end organ disease, such as reducing risk of renal stones (Mollerup, 2002) and increasing BMD. The guideline recommends that patients should be referred to a surgeon with expertise in parathyroid surgery if they have confirmed PHPT plus thirst/excessive urination/constipation, osteoporosis/fragility fracture/renal stone, or albumin-adjusted serum calcium >2.85 mmol/L. If the patient has confirmed PHPT but no symptoms or signs then they should be *considered* for surgery.

Individualised assessment should be considered for patients with mild PHPT (Gittoes, reference 3). For example, the balance is in favour of not operating in older patients, and those with a shorter life expectancy. Conversely, surgery is favoured in those with, for example, risk of worsening bone disease or renal function.

Referral for surgery

The 2019 NICE guidelines may be compared with the 2013 4th International workshop consensus statement (Bilezikian, 2014). Serum calcium levels are identical in both. NICE does not use 24 hour urinary calcium above 10 mmol/d as a threshold for referral. Similarly, there is no threshold for eGFR but stones or calcification are indications for surgery. Where things are quite different is that NICE has no upper age threshold for surgery.

If surgery is agreed then ultrasound is usually the first-line investigation to help localise an adenoma if it will inform the surgical approach. However, ultrasound is user-dependent. A second imaging modality, usually sestambi or 4D-CT, may also be used to guide the surgical approach further. If surgery is not applicable then NICE proposes monitoring, with cutoff calcium levels for offering cinacalcet (>2.85 mmol/L if symptoms, >3.0 mmol/L if not).

The type of surgery depends on whether an adenoma has been identified and whether results are concordant. NICE states that intraoperative PTH measurement should not routinely be used in first-time surgery. Because the success rate of surgery is so high, any incremental improvement in surgical outcome with ioPTH is small.

The guidance is given for monitoring patients with PHPT, including those who have had surgery and those who are pregnant, broadly aligns to the recommendations of the 2013 consensus.

What are the main impacts of the NICE guideline?

- Raising awareness of PHPT
- Incorporating high/normal calcium into the algorithm
- No upper age limit for intervention
- No routine ioPTH
- Thresholds for cinacalcet prescribing



Breakout discussion conclusions

Research

- For atypical adenomas, we suggested setting up a group to circulate specimens and collect clinical and histology data in a database
- What is the clinical importance of atypical adenoma (ADA)? Does it turn into cancer? Do we need to worry? Do we need to worry the patients? Does it have clinical implications?
- It would be useful to validate the 3+3 rule to see if it has an impact
- Reanalysis of samples, to look into those where there has been multiple surgery, especially in those with fragmented samples, might be fruitful
- ESE could support meetings and support databases, spread the knowledge of the EURECA database, and encourage surgeons and endocrinologists to use this EURECA database
- We would like to look at the clinical consequences of secondary hyperparathyroidism without an obvious underlying cause such as vitamin D deficiency or CKD
- Is the raised PTH after bariatric surgery due to malabsorption or are there any other causes?
- Does normocalcemic hyperparathyroidism truly exist? Is it a disease or just a biochemical picture?
- Is there a connection between sodium and calcium metabolism; and what is the role of phosphate and sodium intake in secondary hyperparathyroidism?
- How should PTH be lowered in secondary hyperparathyroidism without an obvious reason?
- Can we unify the various assays for PTH measurement, including the new oxidised PTH assay?
- Assess the impact of the NICE guidelines, with baseline values now, and then again after five years to see what had changed
- Important to evaluate how we investigate renal calcium loss, to try to compare 24-hour urine with spot urine to determine which to use
- There is disagreement about use of the calcium creatinine ratio
- The endocrine database, the existing registry for rare endocrine diseases, could be extended to include parathyroid carcinoma
- What is the optimal time to operate on subjects with renal insufficiency who are being evaluated for renal transplantation: are there enough data to support this or is there a need for a study?
- How might tertiary hyperparathyroidism be better evaluated?
- Another surgery-related subject was the relapse rate
- We need longitudinal data on normocalcemic hyperparathyroidism
- What explains persistently high PTH after surgery even in patients who are rendered normocalcemic?
- Is intraoperative PTH measurement useful or not useful?
- What are the best imaging modalities in parathyroid disease?

Management

- How often does fragmented resection occur, and are there differences between countries?
- Additional molecular testing might be used not only for primary diagnosis but also for recurrent disease
- Optimal imaging of PHPT is yet to be established
- Centralisation of care was discussed, including who should operate
- In this discussion about the treatment choices and diagnostic choices it was clear that there was a link between the European and American guidelines and how they are applied locally
- We felt there was a need for more unified guidelines. For example, in atypical adenoma it would be really helpful to have a unified classification of the pathology that people could use in different countries

- We were unsure who needs intensive and structured follow-up and what that follow-up should be
- These patients should be referred to an expert centre if there is doubt
- On the subject of secondary hyperparathyroidism, we thought it really important to have closer collaboration between endocrinologists and nephrologists. The terminology is used in different ways, especially between secondary and tertiary, and we need more guidelines on thresholds for intervention
- We need a workup protocol for what to do when you find an isolated PTH elevation. If serum calcium, phosphate, PTH and 24-hour urine excretion are normal then people may be reassured that this does not need to be looked into further
- Some protocols on what to do when PTH is elevated after bariatric surgery would be beneficial
- Guidance about when to start using vitamin D analogues instead of calciferol would be welcome

Education

- It is important to use terminology correctly in order to avoid confusion
- We discussed the training of pathologists and endocrinologists, and training surgeons to be aware of the possibility of cancer or atypical adenoma. A combined parathyroid event in which endocrinologists can share information with pathologists and parathyroid surgeons was suggested
- For secondary hyperparathyroidism, nephrologists should share information with endocrinologists and with parathyroid surgeons also
- We talked about education of the public, particularly high-risk groups, concerning vitamin D deficiency. Information is not necessarily of good quality. Could PARAT produce good online evidence that is easily understandable but also readily accessible to the public. Vitamin D deficiency in secondary hyperparathyroidism is a real public health issue
- Vitamin D deficiency should be captured by GPs
- There is a huge variety of causes of secondary hyperparathyroidism: does biochemical diagnosis really indicate a disease?
- When a patient has elevated PTH and normal serum calcium, it should not automatically be called normocalcemic hyperparathyroidism. We need to work hard to exclude other causes; think about optimising vitamin D levels, do patients have calcium deficiencies, think about calcium supplementation
- When considering atypical adenoma and parathyroid carcinoma, it is important to centralise these patients to a specialist centre
- Be aware of suspicious clinical features such as age or calcium level
- A correct definition of hyperparathyroidism is important, in particular the distinction between secondary and tertiary forms
- A joint conference between endocrinologists and nephrologists would be valuable to clarify the terminology and improve guidelines
- The list of possible causes of secondary hyperparathyroidism is too long to be useful for GPs
- The NICE guidelines are helpful, and a useful practical guide on what to think about when investigating these patients. It could be a good example to follow for those countries in which guidelines do not always include the costs of some procedures
- Secondary hyperparathyroidism is an adaptive response, not a disease

Stakeholder engagement

Get involved at:
www.es-e-hormones.org/parat

The PARAT programme of activities adapts over time to reflect leading expert opinion and their collaborative conclusions regarding parathyroid scientific research developments and day-to-day clinical practices.

PARAT is building a community of experts, educators and other key stakeholders as local ambassadors, who help the Steering Group identify recommended next steps to implement improved management practices, education and research. We welcome further endocrinologists, endocrine surgeons, other associated health care professionals and all trainees, to become a stakeholder in PARAT to benefit from the following activities:



Explore ESE Official PARAT Publications

- 1st ESE Consensus statement on Parathyroid Disorders. (Euro J Endocr (2019) 181:3, p1-19)



Respond to Surveys, Research Audits and Polls

- Provide your own perspectives and promote the survey links to others in your local community.



Register to receive the Calcium and Bone Digital Newsletter

- View insights from each Guest Editor on PARAT and other trusted parathyroid sources.



Access ECE On Demand at www.eceondemand.org

- Features all 2017, 2018 and 2019 European Congress of Endocrinology content



Digital Updates. Visit: www.es-e-hormones.org/parat

- Access all related digital materials via the website and our social media channels.



2020-2021 Plans

As a result of the findings from the 1st and 2nd Expert Workshops on Parathyroid Disorders, the Steering Group has begun prioritising which recommended conclusions can be turned into actions during 2020-21.

Supported by its existing PARAT ambassadors, new endocrine experts, other clinical communities, plus the input of other parathyroid disorder stakeholders and online survey results, the PARAT programme will continue to expand, subject to future funding.

To consider how you may wish to join this growing PARAT community, please read our conclusions to the first 2 years of activity summarised in Future Engagement and Recommended actions.





Future Engagement and Recommended actions

Methodology

To conclude the 2nd Expert Workshop, participants were given the opportunity in groups, to reflect upon all PARAT presentations and discussions from 2018-19. They then defined what they considered to be the priority management and educational actions or solutions required to tackle the unmet needs of parathyroid disorder care.

For clarity, the recommended actions have been arranged under three parathyroid disorder headings; Hypoparathyroidism, Hyperparathyroidism and Other Parathyroid disorders. Following the findings of the 2nd Expert Workshop on Parathyroid Disorders, the Steering Group has begun prioritising a set of actions for 2020-21 in reaction to the PARAT stakeholder conclusions and on-going findings from online survey work.

To join the growing PARAT community, and keep up to date with its ongoing activities and events, please visit www.ese-hormones.org/parat.

Hypoparathyroidism

Management

General

Create a universal definition of hypoparathyroidism, or at least recognise the different stages of the disease, to overcome the many definitions being used and treat patients appropriately, so as to remove uncertainty around the duration of follow-up and what to measure, for example after surgery.

Medication

- Patients should be seen by those specialists who see such patients regularly, especially in special circumstances such as pregnancy.
- Consider the optimal use of the different calcium products to avoid overuse of such supplements
- Consider the criteria for recombinant PTH treatment given the lack of long-term safety data.
- As the disease changes over time, and does not develop immediately after surgery, what are the long-term treatment recommendations?

Surgery

- Discuss with thyroid colleagues what indicators for total thyroidectomy there are, and guidance on the extent and volume of surgery.
- Using fluorescence looks a promising method to help prevent post-surgical hypoparathyroidism in the future.

Pregnancy

- Deliver a consensus statement on the treatment of these patients, despite the limited data available. Add a calcium meter in specific groups.

Guidelines vs Guidance

ESE official guidelines are commissioned by an established Clinical Committee process, based upon the literature and other evidence available justifying a perceived educational need.

In contrast, ESE expert opinion led consensus statements or best practice recommendations are made possible through the work of the Focus Area leads and other stakeholders, on any given topic.

Guidance and Evaluation

- Is there sufficient evidence yet to change the 2015 guidelines, to accommodate recommended follow up on urinary calcium levels during treatment
- Acute management of hypocalcaemia versus existing ones on chronic HypoPT
- Long-term outcomes according to treatment, including calcium and vitamin D supplements, focusing on different domains. Can ESE/ PARAT catalyse a collaborative study among different countries on the impact of long-term PTH treatment?
- How can we improve diagnosis of patients as a first step in treatment?
- Better monitoring of disease by testing for calcium, to identify which targets to address or what calcium level to strive for.
- Consideration of the use of PTH in non-surgical hypoparathyroidism but also during pregnancy.
- Request PARAT stakeholders retrospectively gather their opinions regarding previous PHPT pregnant patients, and start prospectively recording data about their own cohort of patients with PHPT in pregnancy.
- From this evidence, construct a set of recommendations on hypoparathyroidism patient management and pregnancy

Education

Targeting appropriate audiences

Different modes of education are needed to target sub-groups of colleagues and patients. ESE should carry out an EU survey identifying the extent and variety of education practices in different countries, to align those approaches better for high risk patient groups?

Clinical colleagues

Surgeons

- Regarding perioperative procedures for thyroid surgery, including how they educate their patients, describing symptoms, risk factors and post-operative management.
- Advice needed for treating hypoparathyroid patients under special circumstances such as bariatric surgery, emergency situations and planned elective surgery.
- Organise a joint meeting between endocrinologists and endocrine surgeons to highlight specifically hypoparathyroidism as a complication of Thyroid Surgery.

Gynaecologists

- Raise awareness regarding pregnancy in patients with hypoparathyroidism

Endocrinologists

- Heighten awareness on genetic causes and stressing the importance of the patient's history to correctly manage the disease.
- Define how to correctly diagnose hypoparathyroidism, including the so-called resistant hypoparathyroidism.
- Advocate and disseminate all current guidelines that exist and develop new educational methods such as e-learning, webinars and slide sets for all physicians managing hypoparathyroid patients, especially useful for those not seeing such patients regularly

Trainees

- Make any necessary recommendations to amend the general calcium and phosphate diseases curriculum. A rolling programme for doctors in training was suggested.
- Create and regularly update a definitive ESE slide set for use by international student schools. This could be linked to CME accreditation, maybe using online resources.

Engaging patients over time

There is a need for an ESE patient education strategy and resultant tactics and materials to support such an initiative. Developing this in association with patient advocacy groups (PAG) and real patients, would provide a single voice on the topics under discussion, whilst alleviating PAG reliance on industry support.

Patient initiatives

- Provide a broad understanding of their disease, such as symptoms of hypocalcaemia, dietary restrictions regarding sodium and heighten awareness to look after their kidneys
- How to react when symptoms of hypocalcemia and hypercalcemia present
- Raise specific awareness for pregnant women with HypoPT to contact their GP and endocrinologist
- Overall, to seek support from their doctors and provide feedback on their symptoms to help build our professional understanding of best practice management



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Hyperparathyroidism Management

Improve treatment standards

- Definition of hyperparathyroidism is an issue, with labels of primary, secondary and tertiary. Should the term “tertiary hyperparathyroidism” be abolished?
- Cinacalcet is used inappropriately; we need a statement on its use.
- Normocalcemic PHPT is a major problem, though GPs should not measure PTH levels if the calcium is normal. In Denmark there is a package of tests done for osteoporosis; if PTH is left out then cases of hyperpara would be missed. A consensus statement on normocalcemic PHPT would be welcome.
- When to start medical therapy in cases with severe osteoporosis?
- Clarification on how to differentiate FHH from primary hyperparathyroidism, to overcome uncertainty.
- Consider how ESE can facilitate a directory of reference pathologists in each country for parathyroid carcinomas, and potentially evaluate the benefits of centralisation of parathyroid carcinoma care, to elevate best practice management.
- Good trial to determine the cost-effective procedures in patients with so-called mild primary hyperparathyroidism. As a corollary of this we need to know how the guidelines that are periodically delivered have been taken up by specialists and also by GPs.
- We should expand upon the concept of serum calcium for the GP, as every patient has an individual range.

Pregnancy

- A call for simple, sensible advice.
- Do endocrine surgeons include special management of pregnant patients in their guidelines?
- Consideration for parathyroidectomy before pregnancy, for PHPT young women?
- Request PARAT stakeholders retrospectively gather their opinions regarding previous PHPT pregnant patients, and start prospectively recording data about their own cohort of patients with PHPT in pregnancy. From this evidence, construct a set of recommendations on hyperparathyroidism patient management and pregnancy.

Improving Diagnosis and Surgical intervention

- We should revise the 10 year old imaging management guidelines.
- Need new guidelines on when to request a genetic test, including a subtopic of how to manage the hereditary forms of this disease, especially in children and young adults. When should you start monitoring, and what are the intervals between monitoring? GPs need to be more aware of genetic predisposition to parathyroid disease and in which situations to refer for genetic testing.
- Can ESE facilitate collating a centralised list of specialists by country, to which blood samples can be sent for genetic testing and to explain the results?
- Define what we mean by recurrence of PHPT and how to manage this both in terms of diagnostic evaluation and operative procedures.
- Also we discussed what to do with isolated elevation of PTH.
- Surgeons should improve their technique whilst performing thyroid surgery, to decrease the frequency of post-operative hypoparathyroidism. There should be standardisation of endocrine treatment after surgery.
- Does biopsy of the parathyroid glands destroy the glands? We should avoid unnecessary biopsies (of all four glands) during surgery.
- Familial PHPT; how to deal with problems in surgical management



- Does biopsy of the parathyroid glands destroy the glands? We should avoid unnecessary biopsies (of all four glands) during surgery.
- Familial PHPT; how to deal with problems in surgical management

Guidelines

- NICE guidelines are important and feel we need to have good management guidelines on when to operate if the patient has recurrence.
- We have a need to develop guidelines in support of when to use genetic tests, how to treat pregnant women, and one on overall treatment of primary hyperparathyroidism.
- ESE decisions on creating a hyperparathyroidism guideline and updating the current primary hypoparathyroidism guideline, are pending.
- A new study on levels of compliance to surgical guidelines would be welcome, given adherence in certain countries is as high as 50%, despite patients actually not fulfilling the diagnostic criteria for primary hyperpara. This is not an isolated issue with guidelines – compliance is a general problem

Education

Improve GP awareness on:

- Misdiagnosis of primary hyperparathyroidism in terms of hypercalcemia.
- Repeated use of vitamin D; how long to wait before re-measuring or seeking expert opinion.
- Improve awareness of what PHPT is in its different forms and calcium dysregulation overall
- If the physician is in doubt, the patient should be referred to a specialist or expert centre.

Health care professional awareness:

- Urologists, dentists and others on calcium dysregulation to help diagnose patients earlier.
- Gynaecologists and paediatricians on awareness of problems in pregnancy, and measurement of calcium levels, considering transient hypocalcemia in newborns.
- Nephrologists to screen patients with kidney stones more generally
- Medical students and endocrinology/internal medicine trainees, plus interns and surgeons about the symptoms and biochemistry of hyperparathyroidism, and how to use the albumin-corrected calcium value.
- Endocrinologists to build confidence of using surgery for PHPT, whilst helping them to advise their patients that such surgery may not exceptionally improve their symptoms
- Important to educate never to operate on a patient who is vitamin D-deficient and that people should be aware of hungry bone syndrome.
- Patients are sometimes referred back when their PTH levels are still elevated.

Tactics

- Define an expert consensus on treatment of patients in pregnancy.
- A simple information sheet on what FHH is and how to treat it.
- Develop a comprehensive set of slides on hyperpara to educate non-expert colleagues
- Highlight laboratory red flag abnormal calcium level values to warn GPs, alongside interpretation tools to deduce what such calcium values infer.

- Patient information on the ESE website to include checklists and questionnaires to educate the patients about hyperpara and pregnancy.
- A multidisciplinary meeting involving calcium and bone specialists with endocrine surgeons, could develop the best modality of how to handle patients when multi-glandular disease is suspected or if the histopathological diagnosis points to atypical adenoma.
- Emphasise the biochemistry as well as imaging as a diagnostic test.



Other Parathyroid Disorders: Education and Management

Management

Causes, Diagnosis and Treatments

- When in doubt about familial disease, especially if genetic testing results are negative, test the whole family. Endocrinologists should be aware that there are families with parathyroid disease.
- Consider the causes of secondary hyperparathyroidism; when should we use the new-generation PTH assessment?
- Diagnosis of FHH should be based on urinary excretion of calcium and the family history vs. extensive family testing. When should we use genetic testing?
- A need for better predictive and diagnostic tools for parathyroid cancer, such as genetic drivers, liquid biopsies and imaging procedures.
- How to diagnose, and then treat patients with autoimmune parathyroid disorders.
- There is a need for an algorithm for genetic testing: when to test, which genes if there is a suspicion of a familial form, and in what order.
- Establish reference centres for pathology samples to be assessed especially with regard to the atypical adenomas and parathyroid cancer.
- Should the cut-off age be 35 to do genetic testing in patients with suspected familial disease? What to do when genetic testing is negative. We need to emphasise in outpatient clinics that the family history is very important – how do we follow patients with ADA.
- How to manage autosomal dominant hypocalcemia.
- New therapies for long-term survivors of parathyroid carcinomas, including the recent checkpoint inhibitors.

Experts and Reference centres

- Endocrinologists need input from nephrologists, and vice versa, in managing patients. How can nephrologists and endocrinologists work together to decide when patients with chronic kidney disease and persistent secondary hyperparathyroidism, go for surgery?
- Create an experience sharing platform to upload rare phenotypes of patients and create a virtual histopathological atlas that could be used to see whether patients fit this profile.
- Set up biobanks in order to develop preoperative tools and biomarkers, especially for parathyroid carcinoma versus atypical adenoma.

Experts and Reference centres

- Endocrinologists need input from nephrologists, and vice versa, in managing patients. How can nephrologists and endocrinologists work together to decide when patients with chronic kidney disease and persistent secondary hyperparathyroidism, go for surgery?
- Create an experience sharing platform to upload rare phenotypes of patients and create a virtual histopathological atlas that could be used to see whether patients fit this profile.
- Set up biobanks in order to develop preoperative tools and biomarkers, especially for parathyroid carcinoma versus atypical adenoma.
- Use standardised terminology around the histomorphometry of atypical adenoma, and creation of a simplified template so that you can compare them between different countries.
- When we have a very rare disease case in relation to the parathyroid glands, we can now go to one of the expert PARAT colleagues as a result of our meetings

Education

Expert engagement

- Highlighting all the different causes of secondary hyperparathyroidism that can lead to high PTH levels, preventing the incorrect diagnosis of normocalcemic hyperparathyroidism.
- Importance of vitamin D deficiency and how to correct and treat it.
- Identify the experts in the field who could receive specimens for second revision.
- Improving the terminology of hyperparathyroidism – possibly removing the term secondary hyperpara in favour of something like “reactive PTH increase”.
- How can we make surgical pathology forms for the treatment of hyperpara.

Patient education

- Educate patients on the differences between thyroid and parathyroid glands and how important their family history can be in patients with these illnesses.
- Increase awareness of the different familial forms and the possible coexistence of pituitary problems and other diseases.
- Especially relevant to raise awareness amongst GPs about rare diseases of the parathyroid glands.
- For atypical adenomas, it is important to educate people to think of that possibility. It is relevant to think of the family history, and pathology specimens should be sent to a specialised centre.

Collaborative efforts

- Important to standardise the terminology to help diagnosis and treatment for renal hyperpara between endocrinologists and nephrologists.
- Improved coordination during preparation of nephrology guidelines in relation to parathyroid diseases.
- Working with surgeons when a parathyroid carcinoma is suspected to improve the best surgical approach.
- Create more awareness among general pathologists about atypical parathyroid adenoma

Parathyroid Carcinoma: Next steps for an ultra-rare disease?

Extracted from Prof. Rajesh Thaker presentation during the 2018 1st Expert Workshop, on the challenges of identifying and managing the ultra rare disorder of parathyroid carcinoma.

Future directions?

We cannot diagnose PC pre-operatively and we rely on surgeons to make the diagnosis. When samples are sent to histology, we cannot sometimes categorically say whether the specimen is a parathyroid carcinoma. We have some medical therapies but we need some better ways to diagnose and treat the disease.

In summary, parathyroid carcinomas are a rare cause of PHPT and they mimic many of the clinical features of parathyroid adenoma. Surgery with en bloc resection of the primary lesion is the only curative treatment, and we need to get these patients to the surgeons with the correct diagnosis. Genetic testing for CDC3 mutations should be offered to all patients with PC as 40% of patients with sporadic PC will have this mutation.

Key recommendations

- We need some better biomarkers to detect these tumours – perhaps we should look at circulating tumour cells and circulating tumour DNA, multiple gene panels. No-one has done proteomic or metabolomic studies in these patients
- We need to perform formal evaluation of parafibromin, Rb, CCND1 and galectin-3 to improve diagnosis and get a better idea about prognosis
- We need to validate the third:second generation PTH assay ratio, which seems quite promising
- As regards treatment, we need some well conducted clinical trials. Perhaps we should consider a trial of mTOR inhibitors, validation of PTH immunotherapy and other immune modulators. In addition, we could see whether temozolomide works. Plus we have access to epigenetic modulators; and 30% of parathyroid tumours have abnormalities of chromatin remodelling or epigenetics



ABSTRACT: Consensus statement

Extracted from *European Journal of Endocrinology* (2019) 181:3, p1



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Unmet therapeutic, educational and scientific needs in parathyroid disorders: Consensus Statement from the first European Society of Endocrinology Workshop (PARAT)

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PARAT, a new European Society of Endocrinology program, aims to identify unmet scientific and educational needs of parathyroid disorders, such as primary hyperparathyroidism (PHPT), including parathyroid cancer (PC), and hypoparathyroidism (HypoPT). The discussions and consensus statements from the first PARAT workshop (September 2018) are reviewed. PHPT has a high prevalence in Western communities, yet evidence is sparse concerning the natural history and whether morbidity and long-term outcomes are related to hypercalcemia or plasma PTH concentrations or both. Cardiovascular mortality and prevalence of low energy fractures are increased, whereas quality of life is decreased, although their reversibility by treatment of PHPT has not been convincingly demonstrated. PC is a rare cause of PHPT, with increasing incidence, and international collaborative studies are required to advance knowledge of the genetic mechanisms, biomarkers for disease activity and optimal treatments. For example, ~20% of PCs demonstrate high mutational burden, and identifying targetable DNA variations, gene amplifications and gene fusions may facilitate personalized care, such as different forms of immunotherapy or targeted therapy. HypoPT, a designated orphan disease, is associated with a high risk of symptoms and complications. Most cases are secondary to neck surgery. However, there is a need to better understand the relation between disease biomarkers and intellectual function and to establish the role of PTH in target tissues, as these may facilitate the appropriate use of PTH substitution therapy. Management of parathyroid disorders is challenging, and PARAT has highlighted the need for international transdisciplinary scientific and educational studies in advancing in this field.

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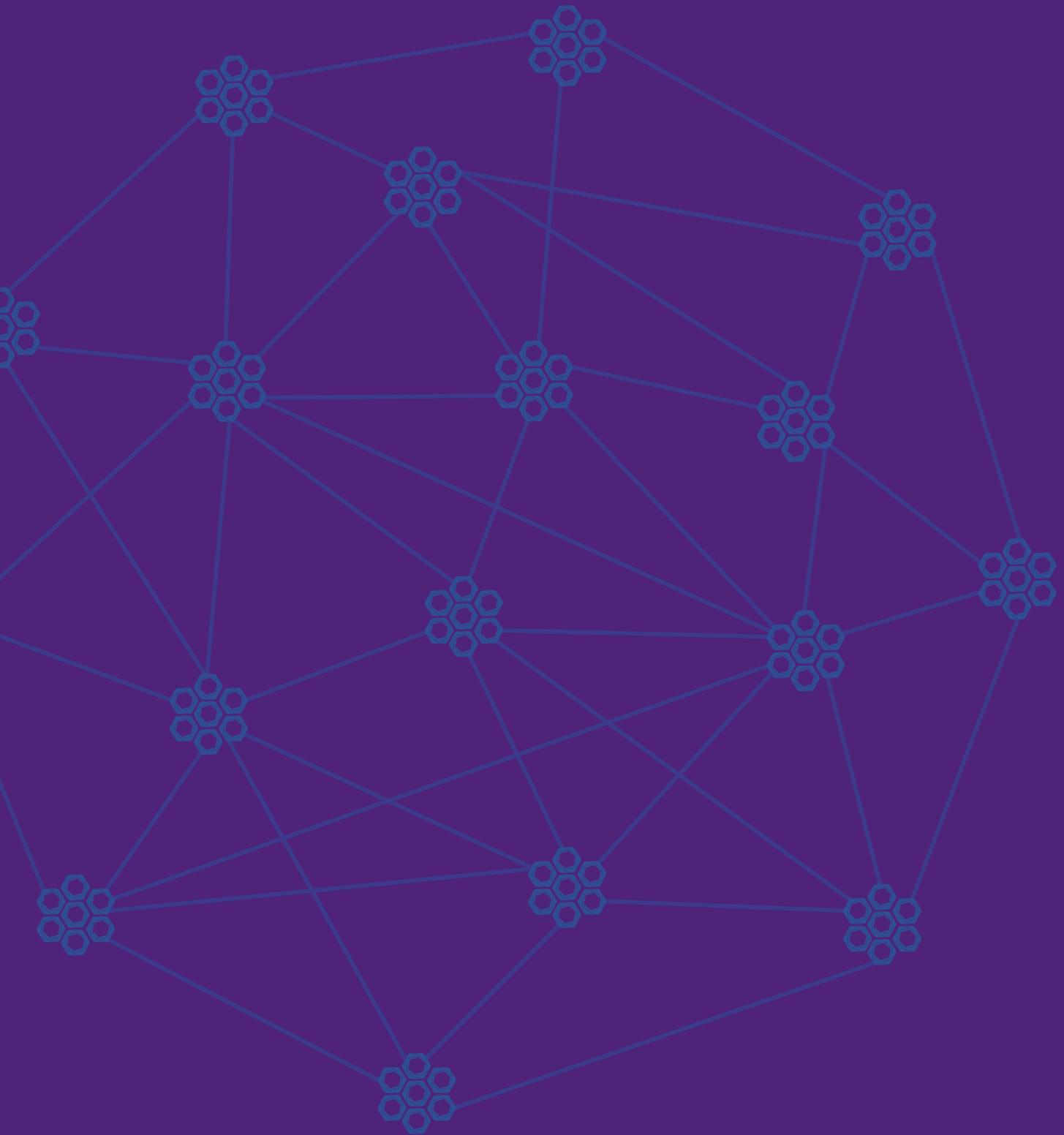
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